Original Article

Germ Cell Tumors in 46, XY Gonadal Dysgenesis

Raiz A. Misgar, Sajad U. Islam Mir, Mohmad H. Mir[1], Mir I. Bashir, Arshad I. Wani, Shariq R. Masoodi

Departments of Endocrinology and [1]Medical Oncology, Sher-i-Kashmir Institute of Medical Sciences, Srinagar, Kashmir, India

Abstract

Introduction: To present the clinical data, investigative profile, management, and follow-up of patients with 46, XY gonadal dysgenesis with germ cell tumors from the endocrine unit of a tertiary care university hospital. **Materials and Methods:** This retrospective study included 3 cases of 46, XY gonadal dysgenesis with germ cell tumors evaluated and managed at the Department of Endocrinology, Sher-i-Kashmir Institute of Medical Sciences, Srinagar, Kashmir, over a period of 13 years from (September 2008 to December 2021). **Results:** Over a period of 13 years, we diagnosed and managed 7 patients with 46, XY gonadal dysgenesis. This included 4 patients with pure gonadal dysgenesis (PGD; Swyer syndrome), 2 patients with mixed gonadal dysgenesis (MGD), and one patient with partial gonadal dysgenesis. Out of these 7 patients, three patients developed germ cell tumors, one patient with MGD, and two patients with pure PGD (Swyer syndrome). In all three patients, germ cell tumor was the first presentation of DSD. The patient with MGD presented with primary amenorrhea and virilization, while the two patients with PGD presented as phenotypic females with primary amenorrhea and pelvic mass. All three patients developed seminomatous cancers. Patient with MGD developed seminoma and the two patients with PGD (Swyer syndrome) developed dysgerminoma. The patients were managed with bilateral gonadectomy with removal of the tumor. In addition, the 2 patients with PGD (Swyer syndrome) received combined chemotherapy. On a follow up ranging from 1 to 10 years, all three patients are disease free. **Conclusions:** we conclude that germ cell tumors may be the first presentation of 46, XY gonadal dysgenesis. In all phenotypic females with primary amenorrhea and dysgerminoma, karyotype is a must to uncover the diagnosis of PGD. In addition virilization may be clue to the presence of germ cell tumor in a patient with 46, XY gonadal dysgenesis.

Keywords: 46, disorders of sex development, dysgerminoma, germ cell tumors, seminoma, XY gonadal dysgenesis

Introduction

Disorders of sex development (DSD) are defined as congenital conditions in which development of chromosomal, gonadal, or anatomical sex is atypical.[1] The incidence of DSD is 1:4500 to 1:5000 live births.[2,3] In addition to the more common and sometimes life threatening medical issues, the significantly increased risk for developing germ cell tumors (GCTs) is of paramount significance in DSD. The risk for development of GCTs is significantly different in the sub-groups of DSD patients. Patients with 46, XY gonadal dysgenesis are at high risk for the development of GCTs.[4,5] Here in, we report three patients, one patient with mixed gonadal dysgenesis (MGD) who developed seminoma and two patients with pure gonadal dysgenesis (PGD; Swyer syndrome) who developed dysgerminoma.

Materials and Methods

This retrospective study included 3 cases of 46, XY gonadal dysgenesis with germ cell tumors evaluated and managed at our center over a period of 13 years from September 2008 to December 2021. The clinical evaluation included detailed history and physical examination. Physical examination focused on anthropometry and abdominopelvic examination. Local genital examination focused on phallic length, palpable gonads and their location, position of urethral opening or presence of common urogenital sinus, labioscrotal folds with degree of fusion, and rugosity of scrotum. All our patients had a karyogram; a minimum of 20 metaphase chromosomes were examined in each case. The hormones (FSH, LH and total testosterone) were measured by DXI 800, Beckman

Access this article online

Quick Response Code:

Website: https://journals.lww.com/indjem/

DOI: 10.4103/ijem.ijem_373_22

Address for correspondence: Dr. Raiz A. Misgar, Additional Professor, Department of Endocrinology, Sher-i-Kashmir Institute of Medical Sciences, Srinagar, Kashmir, India.
E-mail: drreyaz07@rediffmail.com

Submitted: 25-Sep-2022 **Published:** 30-Jun-2023
Accepted: 15-Feb-2023

How to cite this article: Misgar RA, Islam Mir SU, Mir MH, Bashir MI, Wani AI, Masoodi SR. Germ cell tumors in 46, XY gonadal dysgenesis. Indian J Endocr Metab 2024;28:424-8.

Coulter Chemiluminescence Random access analyzer (Brea/CA) following the manufacturer's protocol. All three patients underwent abdominopelvic MRI or CECT for localization of gonads, presence of mullerian structures, and delineation of tumor size and extend. The patients underwent bilateral gonadectomy with removal of tumor and resection of mullerian structures. The resected tissue was subjected to histopathological examination.

A diagnosis of pure gonadal dysgenesis was made in presence of female phenotype, tall stature with eunuchoid body proportions, 46, XY karyotype, streak gonads and elevated gonadotropins. A diagnosis of MGD was made in presence of ambiguous genitalia, simultaneous existence of a streak gonadal band, and testis and mullerian structures on the side of streak gonad.

Ethical aspects

The study was approved by Sher-i-Kashmir Institute of Medical Sciences Committee vide letter no. "IEC/ SKIMS Protocal # RP 198/2021" dated 15/10/2021. Written informed consent was obtained for participation in the study and use of the participant data for research and educational purposes. The procedures follow the guidelines laid down in the Declaration of Helsinki 1964 and as revised later.

Results

Case 1

A 22-year-old patient reared as female was referred to us for the evaluation of primary amenorrhea and virilization. Past medical history was significant for voice change and appearance of pubic and axillary hair at the age of 8 years. Physical examination showed absence of breast development and adult axillary and pubic hair (Tanner stage V). Genital examination revealed clitoromegaly, fused labioscrotal folds, blind vaginal pouch, and non-palpable gonads. On anthropometry height was 150 cm (<3rd percentile), weight 46 kg (<3rd percentile) and arm span 148 cm. The serum gonadotropins were elevated, FSH (59.84 and 60.78 IU/L) and LH (22.19 and 15.04 IU/L). The serum total testosterone was 199.5 ng/dl and 17-OHP progesterone 2.03 ng/ml. MRI of pelvis revealed left hemi-uterus, no gonad on the left side, and a 2.2 × 1.4 cm oval structure (likely testis) on the right side. On diagnostic laparoscopy left hemi-uterus with fallopian tube, 2 × 2 cm right sided testis and 1 × 1 cm left streak gonad were visualized. The chromosomal analysis demonstrated a 46,XY karyotype (SRY +). Bilateral laproscopic gonadectomy and hysterectomy was undertaken. Histopathology of right gonad reported features of seminoma along with atrophic testicular seminiferous tubules and abundant calcification without lymphovascular space invasion and wolffian duct derivatives in the form of epididymis and vas deferens [Figure 1]. Histopathology of left gonad reported fibrocollagenous tissue and fallopian tube.

In view of ambiguous genitalia, simultaneous existence of a streak gonadal band and testis mullerian structures on the side of streak gonad a diagnosis of MGD was made. The patient is disease free after 1 year of follow-up.

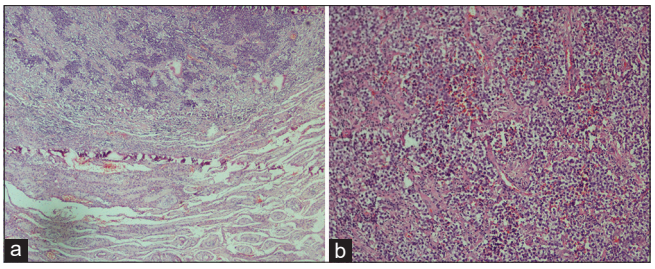

Figure 1: (a) Upper part showing seminoma sharply demarcated from the lower part showing atrophic seminiferous tubules; (b) Section showing Sheets of seminoma cells separated by fibrovascular septa infiltrated by lymphocytes (hematoxylin and eosin, ×10; b, hematoxylin and eosin, ×40).

Case 2

A 16-year-old phenotypically female individual was referred to us for the evaluation of primary amenorrhea and pelvic mass. On physical examination, there was no breast development with sparse axillary and pubic hair and infantile female-type external genitalia. A pelvic mass was palpable on the right side. On anthropometry height was 171 cm (>97th percentile), weight 71 kg (90-97th percentile), and arm span 176 cm. The hormonal evaluation revealed elevated serum FSH (132.53 IU/L) and LH (52.71 IU/L). The serum testosterone was <25 ng/dl. The chromosomal analysis demonstrated a 46, XY karyotype SRY (+). Abdominopelvic MRI showed a large pelvic abdominal mass with dense calcifications. At laparotomy, the intraoperative findings revealed hypoplastic uterus, a streak gonad on the right side, and a huge mass in the left gonad filling lower abdomen with increased vascularity. The fallopian tube was adherent to the mass with no evidence of metastasis or nodal involvement. The patient was subjected to total abdominal hysterectomy and bilateral salpingo-gonadectomy. Histopathology demonstrated typical features of dysgerminoma in the left gonad. The monomorphic population of tumor cells was arranged in diffuse sheets as well as in vague nests pattern separated by delicate fibrous septa infiltrated by lymphocytes. The individual tumor cells were round to polygonal having coarse nuclear chromatin, occasionally prominent nucleoli and clear cytoplasm [Figure 2]. Calcification was seen. Fallopian tube and omentum were uninvolved. Histopathology of right gonad reported streak gonad without evidence of malignancy. The tumor was staged as T1aNxMx-stage 1A and FIGO stage 1A. The patient is disease free after 10 years of follow-up.

Case 3

A 40-year-old female was referred to the department of medical oncology of our institute for evaluation of retroperitoneal mass detected during work up for abdominal and back pain. She was married for 20 years with primary amenorrhea. On clinical examination, there was no breast development, sparse axillary and pubic hair, and infantile female-type external genitalia with blind vaginal pouch. A large mass was felt

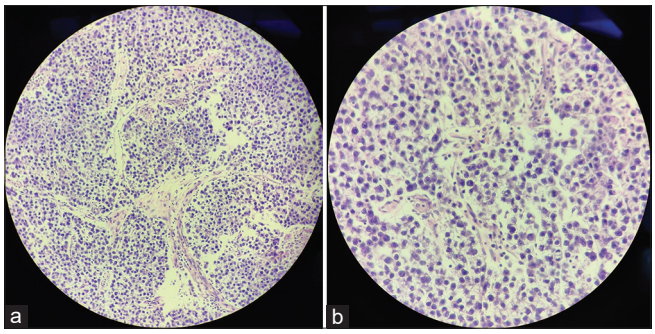

Figure 2: Monomorphic population of tumor cells arranged in diffuse sheets as well as in vague nests pattern separated by delicate fibrous septa infiltrated by lymphocytes. The individual tumor cells are round to polygonal having coarse nuclear chromatin, occasionally prominent nucleoli and clear cytoplasm (a, hematoxylin and eosin, ×20; b, hematoxylin and eosin, ×40).

on the left side of abdomen. Anthropometry revealed height of 172 cm (>97th percentile), weight 65 kg (90th percentile), and arm span of 178 cm. The hormonal evaluation revealed elevated serum FSH (136.72 IU/L) and LH (71.42 IU/L); the serum testosterone was 55 ng/dl. The chromosomal analysis demonstrated a 46, XY karyotype (SRY+). CECT Abdomen and pelvis demonstrated a large, 8.6 × 9.2 cm, lobulated heterogeneously enhancing retroperitoneal mass, encasing the aorta and left renal artery, extending superiorly up to celiac axis and inferiorly up-to the aortic bifurcation. The mass was seen to infiltrate the left psoas muscle and there were few enlarged common iliac and internal iliac nodes. On CECT, uterus was infantile but gonads could not be located. Laprotomy revealed a large, hard, vascular retroperitoneal mass lifting greater omentum and stomach. Histopathology of tumor was reported as dysgerminoma. On Immunohistochemistry, the tumor cells were negative for chromogranin, CK, WTI, desmin, Mic 2, LCA, CD20, and EMA.

In view of female phenotype, tall stature with eunuchoid body proportions, 46, XY karyotype, streak gonads, elevated gonadotropins a diagnosis of pure gonadal dysgenesis was made in patients 2 and 3. In both cases following the cytoreductive surgery, four cycles of combined chemotherapy were given in the form of BEP protocol (bleomycin, etoposide, and cisplatin). The patient 2 is disease free after 10 years of follow-up and patient 3 after 8 years of follow-up.

Discussion

DSD is not an uncommon diagnosis in the out-patient endocrinology services. While congenital adrenal hyperplasia (CAH) is the most common cause of 46, XX DSD worldwide, the etiology of 46, XY DSD varies in different geographic regions.[6] From the Kashmir valley, we have previously reported that 5α-reductase type-2 deficiency is the commonest cause of 46, XY DSD.[7] In the management of DSD, several issues are important such as gender assignment, clinical and diagnostic evaluation, surgical and psychosocial management, and sex steroid replacement.[8] In addition, the significantly increased risk for developing GCTs is of paramount significance.[9]

The risk for the development of GCTs is an important factor to deal with in the management of patients with disorders of DSD. The "type II germ cell tumors" are by far the most frequently occurring and feared tumors in patients with DSD. These are of two sub-types seminomatous and non-seminomatous. Seminomatous cancers are further classified as seminoma in the testis and dysgerminoma in the ovary and dysgenetic gonad.[10] Non-seminomatous cancer includes teratoma, yolk sac tumor, choriocarcinoma, and embryonal carcinoma.[10] The development of these invasive tumors is always preceded by the presence of an *in situ* neoplastic lesion—intratubular germ cell neoplasia unclassified (ITGNU) or gonadoblastoma.[9]

The risk for development of GCTs is significantly different in the sub-groups of DSD patients. In general, forms of DSD with impaired or arrested gonadal development have a high risk of GCTs, whereas forms with normal testis development but reduced androgen synthesis or action have a lower risk.[11] At high risk are patients with gonadal dysgenesis (GD) with the GBY region in their genome and intra-abdominal gonads, patients with partial androgen insensitivity syndrome with non-scrotal gonads, and patients with Frasier and Denys–Drash syndromes.[8] At the other extreme are patients in whom the risk of GCTs is exceptionally low; these include patients with complete androgen insensitivity, ovotesticular DSD and those with Turner syndrome without Y chromosome.

Gonadal dysgenesis is defined as an incomplete or defective formation of the gonads, as a result of a disturbed process of migration of the germ cells and/or their correct organization in the fetal gonadal ridge. The 46 XY GD may be divided in to 3 categories: PGD, MGD, and Partial gonadal dysgenesis. Individuals with PGD (Swyer syndrome) usually present with infantile female-type external genitalia, tall stature with eunuchoid body proportions, 46 XY karyotype, streak gonads, infantile mullerian structures, and hypergonadotropic hypogonadism.[12] In our series, patients 2 and 3 were diagnosed as PGD. The chief presenting compliant of PGD is primary amenorrhea followed by pelvic mass and/or lower abdominal pain. Patients 2 and 3 presented with these complaints. Patients with PGD have high risk of GCTs; the tumor prevalence has been reported as 30–33%.[4,5,13] Gonadoblastoma is the predominant tumor in patients with GD and it is the precursor lesion of the more invasive tumor dysgerminoma.[9] Coexistence of dysgerminoma and gonadoblastoma is seen in about 50% of cases.[14] In our case series, patients 2 and 3 resulted in dysgerminoma. About 65% of dysgerminomas are stage I at diagnosis. About 85 ~ 90% of stage I tumors are confined to one ovary; 10 ~ 15% are bilateral.[15] Dysgerminoma is the only germ cell malignancy that has this significant rate of bilaterality, other germ cell tumors being rarely bilateral. Also 5% of dysgerminomas are discovered in phenotypic females with 46 XY karyotype; thus in adolescent with dysgerminoima and amenorrhea, karyotype is a must.[16]

MGD is the second most common cause (after CAH) of genital ambiguity. It is characterized by the simultaneous existence of a streak gonadal band and testis (dysgenetic or well developed).[17] The genital ambiguity is marked and 2/3 of such individuals are raised as female. A significant percentage (30%) of patients with MGD has somatic features of Turner's syndrome.[17] In our series, patient 1 presented with genital ambiguity was raised as female and had short stature. The typical karyotype of MGD is 45X/46XY but sometimes it is 46, XY as was in our patient 1.[18] Müllerian derivatives in the form of hemi-uterus and fallopian tube usually persist on the side of the more severely affected gonad. Our patient had hemi-uterus and fallopian tube on the side of streak gonad. The persistence of müllerian derivatives on the side of streak gonad provides critical evidence for the paracrine actions of anti-mullerian hormone on the developing müllerian structures. MGD is a subgroup of DSD patients associated with high risk of GCTs. In a series of patients with MGD, the overall prevalence of germ cell tumors is 15%.[19-22]

Interestingly, the patient 1 developed virilization at 8 years of age and it progressed over period of time to adult male pattern hair growth. We hypothetically attributed this to two mechanisms. First, the production of testosterone by the seminoma; it has been reported that GCTs may produce both male and female sex steroids in 46, XY GD.[23,24] Second, the increased sensitivity of pilosebaceous unit to testosterone. The spontaneous pubertal changes or virilization in an individual with DSD should alert the Endocrinologist to the presence of GCT.

The prevalence of GCTs is increased in patients with DSD containing Y chromosome material in their karyotype and is related to the presence of the testis specific protein-Y encoded (*TSPY)* gene.[25,26] The presence of *SRY* or other sex determining genes is irrelevant in this context. The ectopic position of the (dysgenetic) testis adds to this risk. It is hypothesized that there are two factors that promote survival and proliferation of germ cells residing in an unfavorable environment. These include the prolonged expression of octamer binding transcription factor 3/4 (OCT3/4) and increased expression of TSPY.[9]

As both PGD and MGD are associated with high risk of GCTs, this warrants early prophylactic removal of streak-like and dysgenetic gonads. For patients with stage I dysgerminoma, no additional chemotherapy is indicated. However, patients with advanced stage disease require adjuvant chemotherapy. In addition dysgerminomas are also radiosensitive; radiotherapy is reserved for patients with recurrent and chemo resistant disease.

Conclusions

We conclude and emphasize that both PGD and MGD are associated with high risk of GCTs and warrant early prophylactic removal of streak-like and dysgenetic gonads. For all phenotypic females with primary amenorrhea and dysgerminoma, karyotype is a must to uncover the diagnosis of PGD. In addition virilization may be clue to the presence of germ cell tumor in a patient with 46, XY gonadal dysgenesis.

Acknowledgement

None

Author contributions

RAM and SUIM conceptualised and designed the study. MHM, MIB, AIW and SRM supervised the study. All authors drafted the manuscript and approved the final version of manuscript.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Hughes IA. Disorders of sex development: A new definition and classification. Best Pract Res Clin Endocrinol Metab 2008;22:119-34.
2. Thuyen U, Lanz K, Holterhus PM, Hiort O. Epidemiology and initial management of ambiguous genitalia at birth in Germany. Horm Res Paediatr 2006;66:195-203.
3. Hamerton JL, Canning N, Ray M, Smith S. A cytogenetic survey of 14,069 newborn infants. Incidence of chromosome abnormalities. Clin Genet 1975;8:223-43.
4. Verp MS, Simpson JL. Abnormal sexual differentiation and neoplasia. Cancer Genet Cytogenet 1987;25:191-218.
5. Trobs RB, Hoepffner W, Buhligen U, Limbach A, Keller E, Schutz A, *et al.* Video-assisted gonadectomy in children with Ullrich Turner syndrome or 46, XY gonadal dysgenesis. Eur J Pediatr Surg 2004;14:179-84.
6. Herdt GH, Davidson J. The sambia "Turnim-Man": Sociocultural and clinical aspects of gender formation in male pseudohermaphrodites with 5-alpha-reductase deficiency in Papua New Guinea. Arch Sex Behav 1988;17:33-56.
7. Misgar RA, Bhat MH, Masoodi SR, Bashir MI, Wani AI, Baba AA, *et al*. Disorders of sex development: A 10 years experience with 73 cases from the Kashmir Valley. Indian J Endocr Metab 2019;23:575-9.
8. Looijenga LH, Hersmus R, Oosterhuis JW, Cools M, Drop SL, Wolffenbuttel KP. Tumor risk in disorders of sex development (DSD). Best Pract Res Clin Endocrinol Metab 2007;21:480-95.
9. Cools M, Drop SL, Wolffenbuttel KP, Oosterhuis JW, Looijenga LH. Germ cell tumors in the intersex gonad: Old paths, new directions, moving frontiers. Endocrine reviews 2006;27:468-84.
10. Oosterhuis JW, Looijenga LH. Testicular germ-cell tumours in a broader perspective. Nat Rev Cancer 2005;5:210-22.
11. Spoor JA, Oosterhuis JW, Hersmus R, Biermann K, Wolffenbuttel KP, Cools M, *et al.* Histological assessment of gonads in DSD: Relevance for clinical management. Sexual Development 2018;12:106-22.
12. Swyer GI. Male pseudohermaphroditism: A hitherto undescribed form. Br Med J 1955;2:709-12.
13. Hoepffner W, Horn LC, Simon E, Sauerbrei G, Schroder H, Thamm-Mucke B, *et al*. Gonadoblastomas in 5 patients with 46, XY gonadal dysgenesis. Exp Clin Endocrinol Diabetes 2005;113:231-5.
14. Ben Temime R, Chachial A, Attial L, Ghodbanel I, Makhloufl T, Koubaal A, *et al*. 46 XY pure gonadal dysgenesis with gonadoblastoma and dysgerminoma. La Tunisie medicale 2008;86:710-13.
15. Han Y, Wang Y, Li Q, Dai S, He A, Wang E. Dysgerminoma in a case of 46, XY pure gonadal dysgenesis (Swyer syndrome): A case report. Diagnostic Pathology 2011;6:1-6. doi: 10.1186/1746-1596-6-84.
16. Behtash N, Karimi Zarchi M. Dysgerminoma in three patients with Swyer syndrome. World J Surg Oncol 2007;5:1-5. doi: 10.1186/1477-7819-5-71.

17. Acién P, Acién M. Disorders of sex development: Classification, review, and impact on fertility. J Clin Med 2020;9:3555. doi: 10.3390/jcm9113555.
18. Andrade JG, Guerra-Júnior G, Maciel-Guerra AT. 46, XY and 45, X/46, XY testicular dysgenesis: Similar gonadal and genital phenotype, different prognosis. Arq Bras Endocrinol Metabol 2010;54:331-4.
19. Robboy SJ, Miller T, Donahoe PK, Jahre C, Welch WR, Haseltine FP, *et al.* Dysgenesis of testicular and streak gonads in the syndrome of mixed gonadal dysgenesis perspective derived from a clinicopathologic analysis of twenty-one cases. Hum Pathol 1982;13:700-16.
20. Gourlay WA, Johnson HW, Pantzar JT, McGillivray B, Crawford R, Nielsen WR. Gonadal tumors in disorders of sexual differentiation. Urology 1994;43:537-40.
21. Beheshti M, Hardy BE, Mancer K, McLorie G, Churchill BM. Neoplastic potential in patients with disorders of sexual differentiation. Urology 1987;29:404-7.
22. Donahoe PK, Crawford JD, Hendren WH. Mixed gonadal dysgenesis, pathogenesis, and management. J Pediatr Surg 1979;14:287-300.
23. Fukamatsu Y, Tsukahara Y, Hayashi S, Yoshikawa F, Fukuta T. Bilateral gonadoblastoma producing steroid hormones in a patient with 45, X/46, XY gonadal dysgenesis. Gynecol Obstet Invest 1990;30:189-91.
24. Rzepka-Gorska I, Blogowska A, Zajaczek S, Zielinska D. Germinal cell tumors in young and adolescent girls. Ginekol Pol 2003;74:840-6.
25. Lau Y, Chou P, Iezzoni J, Alonzo J, Komuves L. Expression of a candidate gene for the gonadoblastoma locus in gonadoblastoma and testicular seminoma. Cytogenet Cell Genet 2000;91:160-4.
26. Lau YF. Gonadoblastoma, testicular and prostate cancers, and the TSPY gene. Am J Hum Genet 1999;64:921-7.